WHAT IS CLAIMED IS:

1.   A method of reducing or eliminating the incidence of menopausal symptoms, said method comprising administering to patient in need of said elimination or reduction, a therapeutically effective amount of an estrogen or prodrug thereof in association with administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator or prodrug thereof, said modulator being a different compound from said estrogen and not being a benzothiophene or a phenylindole derivative.

2.   A method of reducing or eliminating the incidence of menopausal symptoms, said method comprising administering to patient in need of said elimination or reduction of risk, a therapeutically effective amount of an estrogen or prodrug thereof in association with administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator or prodrug thereof, said modulator being a different compound from said estrogen and not being a phenylindole derivative, further comprising the step of administering, as part of a combination therapy, a therapeutically effective amount of at least one additional agent selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, an androgenic agent, testosterone, androst-5-ene-3β,17β-diol, 4-androstene-3,17-dione and a prodrug of any of the foregoing additional agents.

3.   The method of claim 1 further comprising administering as part of a combination therapy, a therapeutically effective amount of an androgenic agent.
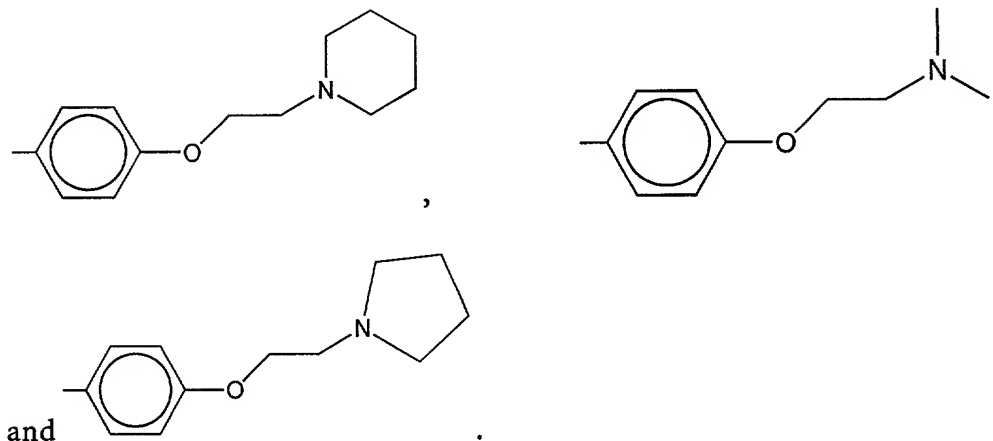
4.   The method of claim 1, wherein the selective estrogen receptor modulator has a molecular formula with the following features :

a) two aromatic rings spaced by 1 to 2 intervening carbon atoms, both aromatic rings being either unsubstituted or substituted by a hydroxyl group or a group converted in vivo to hydroxyl;

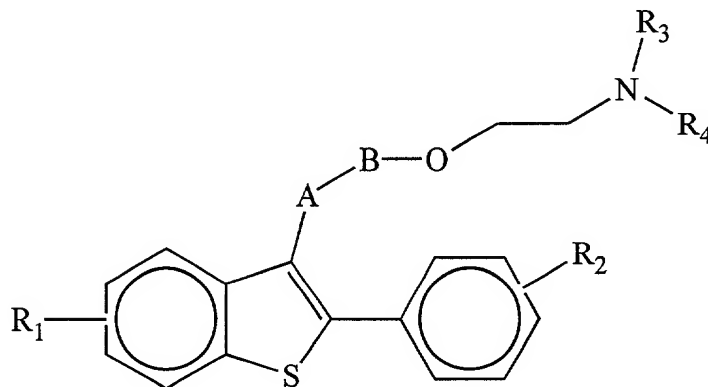b) a side chain possessing an aromatic ring and a tertiary amine function or salt thereof;

and wherein said modulator is not a benzothiophene derivative, a phenylindole derivative, a naphtalene derivative, an isoquinoline derivative or an enantiomeric mixture of 3-phenylquinoline derivatives, or 3-pheynulthiochroman derivatives, 3-phenylchroman derivatives having more than 10% of the enantiomer of 2R configuration.

5. The method of claim 4 wherein the side chain is selected from the group consisting of :

,

and .

6. The method of claim 4, wherein the selective estrogen receptor modulator is selected from the group consisting of a triphenylethylene derivative, benzopyran derivative, HMR 3339, HMR 3656, LY 335124, LY 326315, SH 646, ERA 923 and centchroman derivative.

7.   The method of claim 8, wherein the selective estrogen receptor modulator is a benzothiophene derivative compound of the following formula:

wherein R_1 and R_2 are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl ;
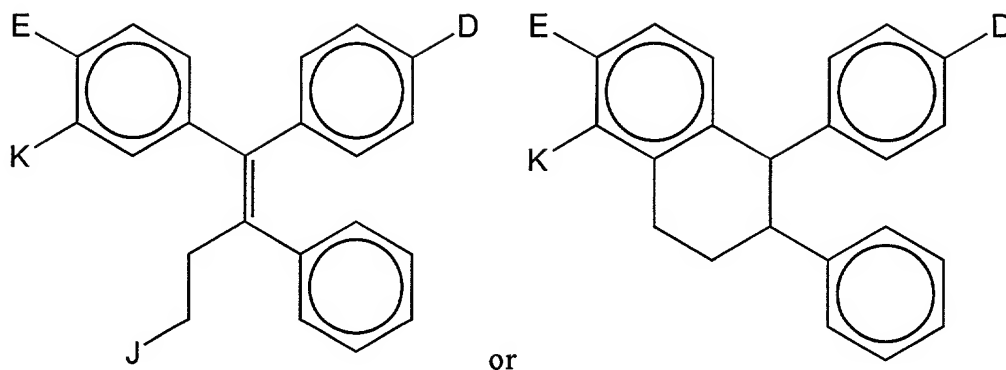
wherein R_3 and R_4 are either (a) independently C1-C4 alkyl, or (b) a moiety which in combination with the nitrogen to which they are bound, is selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino;

wherein A is selected from the group consisting of -CO-, -CHOH, and -CH$_2$-;

wherein B is selected from the group consisting of phenylene, pyridylidene, and -cycloC$_4$H$_2$N$_2$-.

8.   The method of claim 7, wherein the selective estrogen receptor modulator is selected from the group consisting of Raloxifene, LY 353381 and LY 335563.

9.   The method of claim 4, wherein the selective estrogen receptor modulator is a triphenylethylene or diphenylhydronaphthalene derivative compound of the following formula :
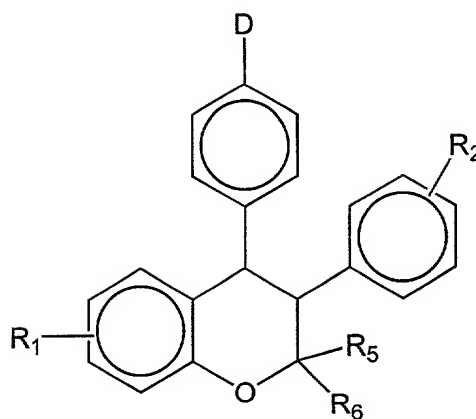
or

wherein D is $-OCH_2CH_2N(R_3)R_4$, $-OCH_2CH_2OH$, or $-CH=CH-COOH$ (R_3 and R_4 either being independently selected from the group consisting of C1-C4 alkyl, or R_3, R_4, and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

wherein E and K are independently hydrogen or hydroxyl, phosphate ester, or lower alkyl, wherein J is hydrogen or halogen.

10. The method of claim 1, wherein selective estrogen receptor modulator is selected from the group consisting of OH-tamoxifen, Droloxifene, Toremifene, Iodoxifene, Lasofoxifene, iproxifene, FC 1271, and GW5638.

11. The method of claim 4, wherein the selective estrogen receptor modulator is a centchroman derivative compound of the following formula :
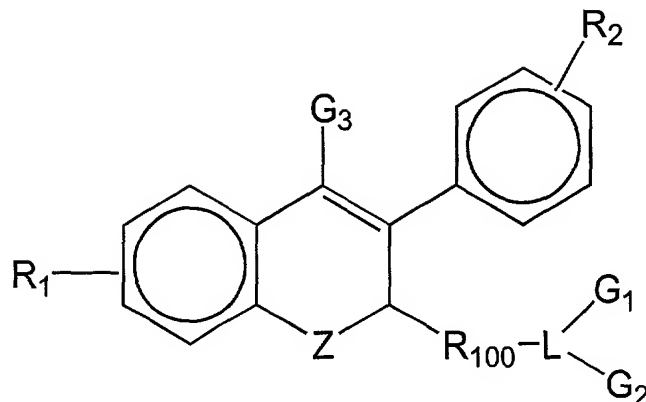
wherein R_1 and R_2 are independently selected from the group consisting of :

hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;

wherein R_5 and R_6 are independently hydrogen or C_1-C_6 alkyl ;

wherein D is -$OCH_2CH_2N(R_3)R_4$ (R_3 and R_4 either being independently selected from the group consisting of C_1-C_4 alkyl, or R_3, R_4 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino).

12.   The method of claim 11, wherein the centchroman derivative is (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

13. The method of claim 4 wherein the selective estrogen receptor modulator has the following formula :

wherein R_1 and R_2 are independently hydrogen, hydroxyl or a moiety which is converted to hydroxyl in vivo ;

wherein Z is either absent or selected from the group consisting of $-CH_2-$,-0-,-S- and $-NR_3-$ (R_3 being hydrogen or lower alkyl) ;

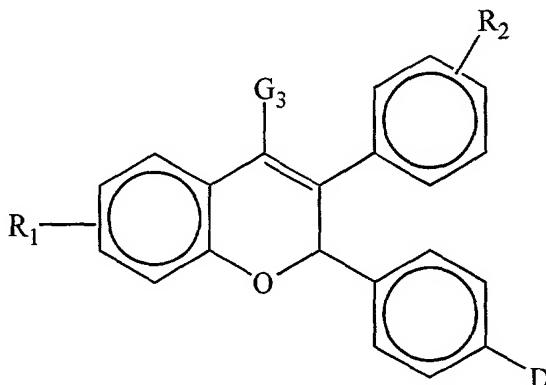wherein theR100 is a bivalent moiety which distances L from the B-ring by 4-10 intervening atoms ;

wherein L is a bivalent or trivalent moiety selected from the group of -SO-, -CON-, -N<, and -SON< ;

wherein G_1 is selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_2 and L is a 5-to 7-membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_2 is either absent or selected from the group consisting of hydrogen, a C_1 to C_5 hydrocarbon, a bivalent moiety which in combination with G_1 and L is a 5-to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing;

wherein G_3 is selected from the group consisting of hydrogen, methyl and ethyl.

14. The method of claim 13, wherein the compound is a benzopyran derivative of the following general structure :
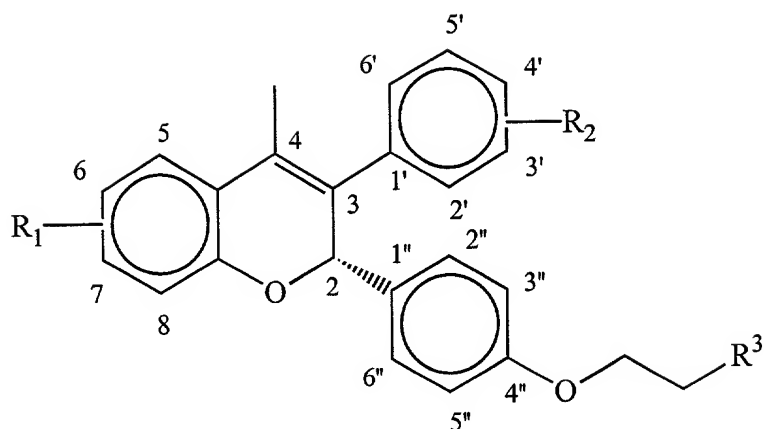

or a pharmaceutically acceptable salt thereof,

wherein D is -OCH$_2$CH$_2$N(R$_3$)R$_4$ (R$_3$ and R$_4$ either being independently selected from the group consisting of C$_1$-C$_4$ alkyl, or R$_3$, R$_4$ and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino);

wherein R$_1$ and R$_2$ are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

15. The method of claim 14, wherein the benzopyran derivative is optically active due to a majority of its stereoisomer having an absolute configuration S on carbon 2, said compound having the molecular structure:
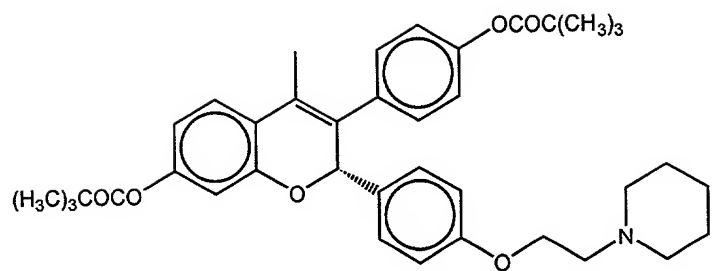
wherein R_1 and R_2 are independently selected from the group consisting of hydroxyl and a moiety convertible in vivo to hydroxyl;

wherein R^3 is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and NRaRb (Ra and Rb being independently hydrogen, straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, and straight or branched C_2-C_6 alkynyl).
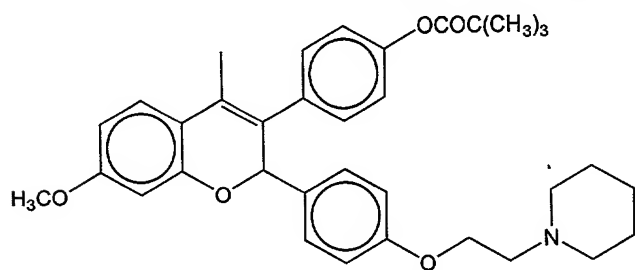
16.   The method of claim 15, wherein said compound or salt substantially lacks (2R)-enantiomer.

17.   The method of claim 15, wherein said selective estrogen receptor modulator is selected from the group consisting of:
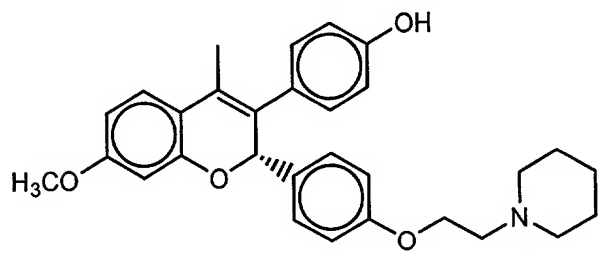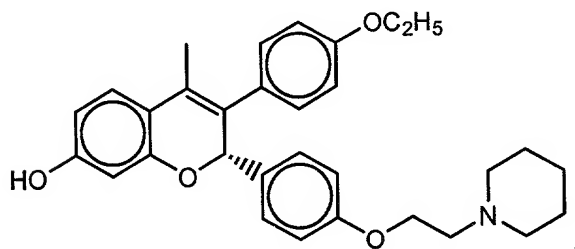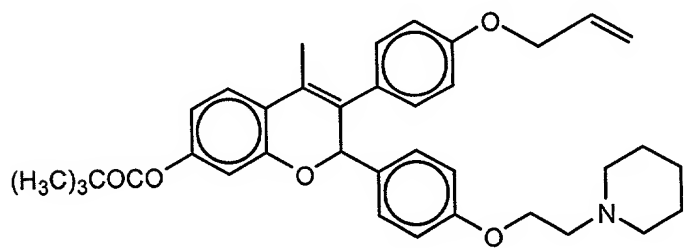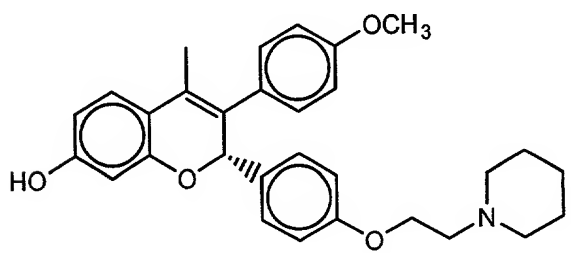
EM-800

EM-1520
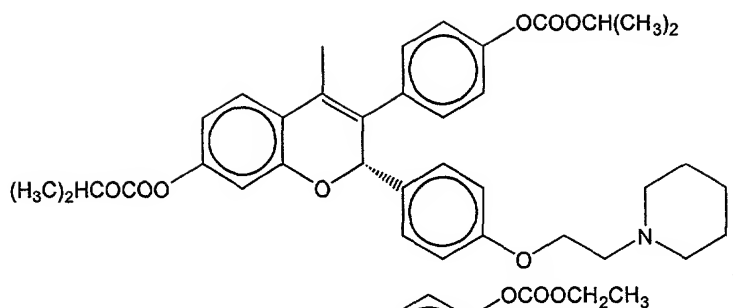

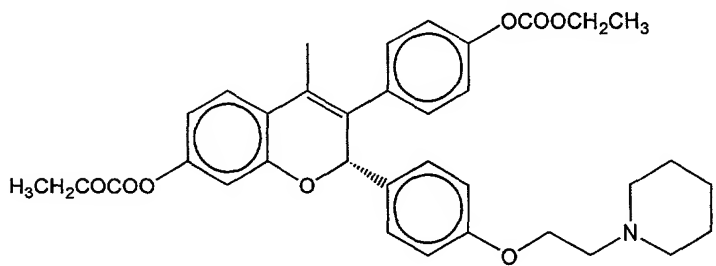**EM-1872**

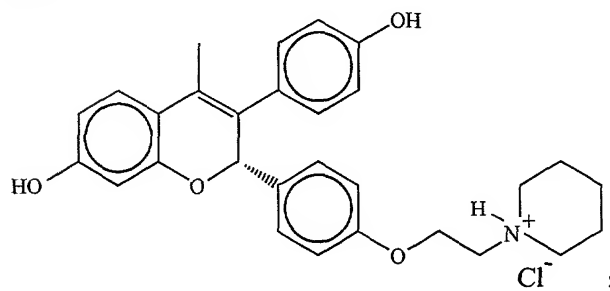**EM-1900**

EM-1901

EM-1903

EM-1533

EM-1518

and

EM-652.HCl
(EM-1538)

wherein all of the foregoing molecular structures whose stereochemistry is indicated are optically active due to a majority of their stereoisomers being of 2S configuration.

18. The method of claim 15 wherein, the benzopyran derivative is a salt of an acid selected from the group consisting of acetic acid, adipic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, hydrochlorothiazide acid, hydroxy-naphthoic acid, lactic acid, maleic acid, methanesulfonic acid, methylsulfuric acid, 1,5-naphthalenedisulfonic acid, nitric acid, palmitic acid,
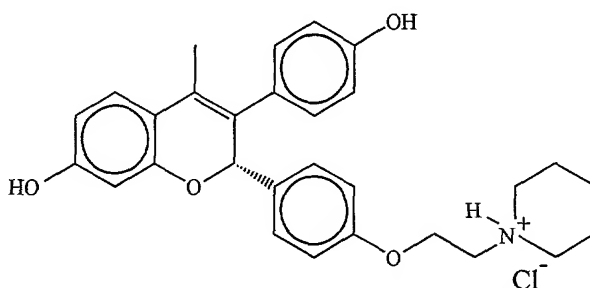
pivalic acid, phosphoric acid, propionic acid, succinic acid, sulfuric acid, tartaric acid, terephthalic acid, p-toluenesulfonic acid, and valeric acid.

19.   The method of claim 18, wherein the acid is hydrochloric acid.

20.   The method claim 1, wherein said selective estrogen receptor modulator is:

EM-652.HCl

(EM-1538)

5   and is optically active due to a majority of its stereoisomers being of 2S configuration; and

wherein the estrogen is selected from the group consisting of 17β–estradiol, 17β–estradiol esters, 17α–estradiol, 17α–estradiol esters, estriol, estriol esters, estrone, estrone esters, conjugated estrogen, equilin, equilin esters, 10   17α–ethynylestradiol, 17α–ethynylestradiol esters, mestranol, and mestranol esters.

21.   The method of claim 1, wherein said estrogen is selected from the group consisting of 17β–estradiol, 17β–estradiol esters, estriol, estriol esters, estrone, estrone esters, conjugated estrogen, equilin, equilin esters, 17α–ethynylestradiol, 17α–ethynylestradiol esters, mestranol, mestranol esters, 5   chemestrogen, DES, phytestrogen, tibolone, 2'-ethylestrogenoxazole, and ethynediol.

22.   The method of claim 1, wherein the selective estrogen receptor modulator has no estrogenic activity in breast or endometrium tissues.

23.   The method of claim 1, wherein said estrogen is a mixed estrogenic/androgenic compound.

24.   The method of claim 23, wherein the mixed estrogenic/androgenic compound is Tibolone.

25.   The method of claim 1, wherein menopausal symptoms are selected from the group consisting of hot flashes, vasomotor symptoms, irregular menstruation, vaginal dryness, headache and sleep disturbance.

26.   The method of claim 1, wherein said treatment reduces the risk of the patients acquiring breast or endometrial cancer.